MEDICAL POLICY AND PROGRAM REVIEW COUNCIL
January 24, 2018, 9:00 AM, WO-Bldg. 2, Room 2058

Lead(s): Valerie Pratt, Division of Nonprescription Drug Products, OND
Andrew Mosholder, Division of Epidemiology I, OSE
Judith Racoosin, Division of Anesthesia, Analgesia, & Addiction Products, OND
Christine Nguyen, Division of Bone, Reproductive, & Urologic Products, OND
Tamara Johnson, Division of Pediatric and Maternal Health, OND

Purpose: Discuss Tracked Safety Issue 1355 for acetaminophen and effects during pregnancy

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Agenda:

I.	Presentation	15 minutes
II.	Discussion	45 minutes

Background:

Acetaminophen (also known by the acronym APAP), which crosses the placenta,[1] is widely used during pregnancy; in two U.S. studies, roughly two-thirds of mothers reported taking acetaminophen while pregnant.[2] In February 2014, an article by Liew in JAMA Pediatrics reported an increased association between acetaminophen use in pregnancy and attention deficit/hyperactivity disorder (ADHD) in the offspring.[3] Hence, TSI 1355 for acetaminophen and effects during pregnancy was opened May 15, 2014. The Division of Epidemiology 1 (DEPI) conducted a review of this publication (RCM # 2014-689) and concluded, "The study's findings are difficult to interpret due to methodologic limitations and in the context of other existing data." DEPI recommended no regulatory action be taken at that time and continued vigilance.

In September 2014, an article by Thompson in PLOS One reported an association between acetaminophen use during pregnancy and ADHD symptoms.[4] At that time, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), Office of Surveillance and Epidemiology (OSE), and Division of Pediatric and Maternal Health (DPMH) had already been working on two other safety issues with analgesic use in pregnancy (NSAIDs and spontaneous abortion, opioids and neural tube defects) and was planning a Drug Safety Communication (DSC). Given the newly emerging issue of ADHD in the children of women who took acetaminophen during pregnancy, the decision was made to add this issue to the DSC. On January 9, 2015, the Agency issued Drug Safety Communication (DSC), *Prescription and Over-the-Counter (OTC) Pain Medicines: Drug Safety Communication – FDA Has Reviewed Possible Risks of Pain Medicine Use during Pregnancy*.[5] With regard to the acetaminophen issue, the DSC stated that data are "too limited to make any recommendations" at this time, and it encouraged healthcare professionals talk with each patient about the benefits and risk of analgesic use during pregnancy, which may differ among patients and by treatment indication.

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[1] Nitsche JF, Patil AS, Langman LJ, et al. Transplacental Passage of Acetaminophen in Term Pregnancy. Am J Perinatol. 2017;34:541-543
[2] Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol 2005;193(3 Pt 1):771-7.
[3] Liew Z et al. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr 2014;168(4):313-320.
[4] Thompson J et al. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. PLOS One 2014;9(9):e108210.
[5] https://www.fda.gov/Drugs/DrugSafety/ucm429117.htm

On March 18, 2015, DEPI completed a second review (RCM # 2015-387) of the literature. It concluded that "whether the association in causal in nature is still uncertain" and "preclinical data may be more informative in that regard."

The Division of Nonprescription Drug Products (DNDP) then consulted Nonclinical for a review of the available data. The February 8, 2016 review concluded, "The available nonclinical data…do not describe studies in animals that were adequately designed and conducted to address the question posed by OSE…at this time, the behavioral responses in animals that are most likely predictive of an ADHD response in humans are uncertain and, therefore, additional animal studies are not likely to be informative".

On March 1, 2016, DNDP, DEPI, and Nonclinical met to discuss the available data and completed reviews. It was agreed that data did not support a causal association between acetaminophen and ADHD at that time and that the TSI would be closed.

Since then, additional publications, including Stergiakouli et al. in the *JAMA Pediatrics*, triggered a re-opening of the TSI.[6]

Discussion:

On October 14, 2016, DEPI completed its review of neurodevelopmental outcomes following prenatal acetaminophen exposure. In addition to the Stergiakouli article, it reviewed three additional studies.[7,8,9] The review concluded that eight observational studies have examined neurodevelopmental outcomes following prenatal acetaminophen exposure. While the quality of the evidence varied across studies, seven showed some association with adverse neurodevelopmental outcomes (e.g., cognitive development, attention problems, motor development, autistic behaviors, and general behavioral problems). The review acknowledged the absence of proof of a causal relationship; recommended seeking nonclinical input regarding whether nonclinical models could address the additional neurodevelopmental outcomes reported with prenatal acetaminophen exposure; and recommended communicating the following points to consumers:

- Current data raise the possibility of neurodevelopmental harm to the fetus from maternal acetaminophen use
- Acetaminophen should be used judiciously during pregnancy; other analgesics are associated with more definite pregnancy risks
- Acetaminophen may be needed to reduce the risks associated with maternal fever

On February 10, 2017, Division of Bone, Reproductive, and Urologic Products (DBRUP) completed its related consult, which concluded:

> *In sum, we acknowledge the consistency of the findings of positive association between APAP and adverse neurodevelopmental outcomes in the majority of the published observational studies reviewed to date. Although we have more studies, we do not have higher quality data to better inform drug causality and what these findings mean in clinical practice. All of these studies had significant limitations, uncertainties, and critical missing information that preclude reliable inference of drug attribution. Thus,*

[6] Stergiakouli E, Thapar A, Davey Smith G. Association of acetaminophen use during pregnancy with behavioral problems in childhood: Evidence against confounding. JAMA Pediatr. 2016 Aug 15. [Epub ahead of print]
[7] Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. Int J Epidemiol. 2016 Jun 28. [Epub ahead of print]
[8] Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal Use of Acetaminophen and Child IQ: a Danish Cohort Study. Epidemiology. 2016 Jul 28. [Epub ahead of print]
[9] Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MM, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. Int J Epidemiol. 2016 Aug 31. [Epub ahead of print]

we are unable to draw any conclusion about the causal association between prenatal APAP exposure and the different adverse neurodevelopmental outcomes, based on the available evidence.

DBRUP does not believe the available observational evidence merits updating the 2015 DSC titled "FDA Review of Possible Risks of Pain Medicine Use During Pregnancy" with more definitive conclusions, such as a "possibility" of causation, about drug causality of APAP and adverse neurodevelopmental outcomes. Nevertheless, we acknowledge the importance of apprising the public about FDA's review of new studies for a safety signal that was a subject of a DSC. Therefore, we believe it is reasonable to consider updating the 2015 DSC to indicate that FDA has evaluated additional publications on APAP and neurobehavioral/developmental outcomes in the offspring. The updated DSC, however, should retain the same FDA conclusion about the inability to draw reliable conclusions about drug causality and clinical recommendations stated in the 2015 DSC.

On April 7, 2017, DPMH completed its consult, which concluded:

The findings of the clinical studies demonstrate some consistency of association among the outcomes related to attention problems and general behavioral problems; however, the studies may only be demonstrating a common finding due to common use of the drug in the pregnant population.

DPMH agrees that some communication is needed to meet the public's expectation of the Agency's assessment of press in August 2016 that we are actively reviewing the new information. The communication would update the data review, while maintaining a balance with the benefits of acetaminophen use. Because there are no alternative OTC medications to manage pain and/or fever during pregnancy, to raise concerns of a strengthened association with "adverse neurodevelopmental outcomes", when important limitations exist for the data and no causal relationship can be established, would have a significant public health impact for the pregnant population and their healthcare providers. An update to the DSC may address immediate inquiries about the recent publications, but care must be taken to avoid invoking more concern than warranted at this time and unintentional repercussions (e.g., no treatment of maternal fever) on pregnant patients and their healthcare providers. Note that the current DSC already communicates the key message and the advice to the public does not change substantially from the January 2015 DSC.

DEPI, DBRUP, and DPMH's recommendations were discussed on February 6 and April 3 and 24, 2017 with DNDP and the following additional Offices/Divisions:

- Division of Pharmacovigilance
- Nonclinical
- DAAAP
- Office of Communications (OComm)
- Office of Media Affairs (OMA)

At these meetings, the following discussion points were raised:

- It is not clear if the variety of neurodevelopmental outcomes that DEPI grouped together (i.e., cognitive development, attention problems, motor development, autistic behaviors, and general behavioral problems) should be grouped together, due to different embryologies, etiologies, etc. Taken separately, there is insufficient data to support regulatory action for an individual outcome. DEPI's response was that neurodevelopmental teratogens typically impact a spectrum of outcomes rather than a single deficit or disorder.[10]

[10] Mendola P, Selevan SG, Gutter S, Rice D. Environmental factors associated with a spectrum of neurodevelopmental deficits. MRDD Research Reviews 2002;8:188–197.

- A critical limitation of the studies was the generally higher prevalence of alcohol use, smoking, or psychiatric/medical illness among mothers who used acetaminophen compared to non-users. Key medical history information, such as family history of ADHD and concomitant diagnoses during pregnancy and early childhood, were also not always available. However, when known, such factors were adjusted for in the analyses, and one positive study[11] employed unexposed siblings as the control group.
- If there is an association between acetaminophen and neurodevelopmental outcomes, it is not clear what dose, duration, and trimester of exposure may result in which outcome. However, several studies related the risk to higher levels of exposure as measured by days of use. As the outcomes do not involve organogenesis, it would not be expected that an association would be observed only for first trimester exposure.
- In the studies that used Hazard Ratios as the metric of risk, the identified Hazard Ratios (HR) were low (i.e., 1.2 – 1.4). These low levels of increased risk, although often statistically significant because of the large size of the databases used in the studies, could represent unmeasured confounding.
- Strengths of the studies included that, in every study, exposure was recorded before the outcome was determined, eliminating recall bias. Also, in some studies, risk appeared related to frequency/duration of use. One completely negative study has been published
- Acetaminophen remains the first-choice pain reliever during pregnancy, as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are associated with other risks.
- If a communication was released, the message should remain unchanged from the January 9, 2015 *Drug Safety Communication – FDA Has Reviewed Possible Risks of Pain Medicine Use during Pregnancy*, which reminded consumers and health care professionals that "the use of pain medicines during pregnancy should be carefully considered". Pregnant women should "always discuss all medicines with their health care professionals before using them…It is important to carefully weigh the benefits and risks of using prescription and OTC pain medicines during pregnancy."
- Websites for pregnant women do not consistently reflect the nuance message of the Agency's 2015 DSC.
- The Office of Communication did not recommend a new communication if the key message is unchanged from the prior DSC and other communications.
- The Agency should clarify (b) (5) .

Accordingly, information was sought regarding the European Medicines Agency (EMA) and American Congress of Obstetricians and Gynecologists (ACOG) position on this issue, which are as follows:

- EMA Pharmacovigilance Risk Assessment Committee (PRAC): In its recommendations dated September 26-29, 2016, PRAC recommended "no action at this stage" regarding paracetamol use in pregnancy and child neurodevelopment (EPITT No. 17796).
- ACOG[12]:
    - CNN's "Acetaminophen during pregnancy may increase risk of hyperactivity in kids": Dr. Hal C. Lawrence, CEO of the American College of Obstetricians and Gynecologists, noted that the current study did not examine significant details, such as the exact dose taken or the reasons why a mother needed to take medication, and behavioral disorders are multifactorial and very difficult to associate with a singular cause
    - ABC's Good Morning America's "Study links acetaminophen to childhood behavioral problems": "During her segment, ACOG Fellow Dr. Jennifer Ashton, MD, says that, according

[11] Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. Int J Epidemiol 2013;42:1702-13.
[12] https://www.acog.org/About-ACOG/ACOG-Departments/ACOG-Rounds/September-2016/ACOG-in-the-News

to ACOG, there is no direct relationship between acetaminophen use and behavioral issues in children."

On November 15, 2017, the working group met again. DEPI discussed another recently completed study by Ystrom, which the group agreed did not alter the overall assessment.[13] Nonclinical presented the findings of its recently completed consult, (b) (5) [redacted]

Consistent with this advice, (b) (5) [redacted]

Options for Discussion

- Communication
  - Pros:
    - Reminds consumers to consult their healthcare professionals before taking medicine when pregnant

[13] Ystrom E, et al. Prenatal exposure to acetaminophen and risk of ADHD. Pediatrics. 2017;140(5):e20163840.

        - Educates consumers about possible neurodevelopmental risk when acetaminophen is used during pregnancy
        - Educates consumers about risks of untreated fever
    - Cons:
        - Drug Safety Communication and Consumer Update already released
        - Due to lack of causal association and clarity regarding the signal (i.e., exposure needed, outcome of interest), the key message would not change substantially from the January 2015 DSC
        - Inadvertent over-attribution of neuro-behavioral risks to acetaminophen on the part of the pregnant women and their providers. Prescribers may be reluctant to advise acetaminophen use when needed. Some pregnant women may not use acetaminophen resulting in untreated fever and pain or may increase use of NSAIDS or opioids, which are associated with other negative outcomes.
- Nonclinical study
    - Pros:
    - Cons:

(b) (5)

(b) (5)

- Close TSI
    - Pros:
        - Acknowledges the lack of a causal association
        - Does not sway analgesic use during pregnancy towards riskier NSAIDs or opioids nor result in more untreated fever and pain
        - Consistent with the following:
            - EMA's PRAC which recommended "no action"
            - ACOG which stated there is "no direct relationship between acetaminophen use and behavioral issues in children"
    - Cons:
        - Additional publications are likely over time
        - Association could be causal

Attachments

- Consults
    - DEPI RCM 2016-1871 (October 14, 2016)
    - DBRUP (February 10, 2017)
    - DMPH (April 7, 2017)
    - Nonclinical (December 4, 2017)
- Table of neurodevelopmental outcome studies following in utero acetaminophen exposure
- Communications
    - Drug Safety Communication: FDA review of possible risks of pain medicine use during pregnancy (January 9, 2015)

    - Consumer Update: Pregnancy: A time for special caution (May 10, 2013)
    - Medicine & Pregnancy
- Klass, Perri. *Does an ADHD link mean Tylenol is unsafe in pregnancy?* The New York Times. Dec 4 2017.

TSI 1355: Acetaminophen and Effects during Pregnancy

January 24, 2018

Valerie Pratt, MD
Deputy Director for Safety
Division of Nonprescription Drug Products

Andrew Mosholder, MD, MPH
Medical Officer
Division of Epidemiology 1

Background: Key Issue

- Acetaminophen is the first choice pain and fever reliever during pregnancy
  - NSAIDs and opioids are associated with significant risks
- Ten observational studies report some association with adverse neurodevelopmental outcomes (cognition, attention, motor function, autism, and general behavior)
- Prior communications warn of possible risks of pain medicine use during pregnancy
- Question: Do the current data justify additional action at this time?

Background: Scientific

- 12 publications describing results from 7 prospective longitudinal mother/child cohorts (1 in US)
- Long term assessments of offspring
  - Ages: 15 mos – 11 yrs
  - Outcomes: ADHD medication use, IQ, behavior ratings, motor and language milestones, continuous performance tasks
- 11 of 12 publications reported some risk of adverse neurodevelopmental outcomes:
  - lower IQ, delayed motor and language development, general behavioral problems, autistic behaviors, and ADHD
  - risk not always found for every outcome in every study that measured it

Limitations of studies

- Main limitation: possibility that confounding accounts for associations reported
  - Modest effect sizes (most risk estimates < 2)
  - Confounding by indication possible
  - Unmeasured confounding
    - 2 studies found some association with paternal use
- Higher prevalence of substance use and mental illness in acetaminophen users
- Inadequate adjustment for genetic disposition, pregnancy complications, and early childhood
- Lack of precision regarding acetaminophen dose, duration, timing of exposure
- Effects clinically significant?

Strengths of studies

- Length of follow-up (up to 11 years)
- In 7 studies, risk correlated with measure of exposure
- All studies determined exposure prior to outcome--avoids recall bias
- Strategies to control for confounding
  - All studies adjusted for measured covariates
  - One positive study (Brandlistuen 2013) used sibling controls
  - Most studies adjusted for APAP indication (e.g., fever, infection, pain) in some way
  - One study (Liew 2016) found interaction between acetaminophen use and fever on IQ (p=0.01)
    - Details on these two studies can be provided if there is interest

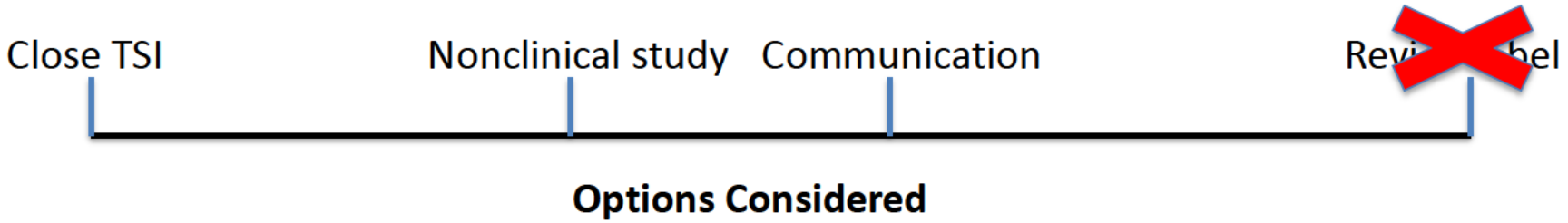
Background: Regulatory

- Acetaminophen is a monograph drug*
  - Lacks current standard developmental and reproductive nonclinical studies
- Communications
  - DSC: FDA Has Reviewed Possible Risks of Pain Medicine Use During Pregnancy (Jan 9, 2015)
  - Consumer Update: Pregnancy: A Time for Special Caution (May 10, 2013)
  - Office of Women's Health: Medicine & Pregnancy
- Consults completed by DAAAP, DBRUP, and DPMH

* Except for intravenous acetaminophen products which are NDAs

Objective of Meeting

- Seek advice on next steps



- Regulatory options:
  - Close TSI
  - Communication
  - Nonclinical study

Option: Communication

- Pros:
  - Reminds consumers to consult their healthcare professionals
  - Educates about possible neurodevelopmental risk and risk of untreated fever
- Cons:
  - Drug Safety Communication and Consumer Update already released
  - Due to lack of causal association and clarity regarding the signal, the key message would not change
  - Inadvertent over-attribution of risk to acetaminophen
    - Prescribers may be reluctant to advise its use
    - Some pregnant women may not use it resulting in untreated fever/pain or increased use of NSAIDS or opioids, which are associated with other negative outcomes

Option: Nonclinical Study

- Pro: (b) (5) [redacted]
- Cons: (b) (5) [redacted]

Option: Close TSI

- Pros:
  - Acknowledges the lack of a causal association
  - Does not sway analgesic use in pregnancy towards riskier NSAIDs or opioids nor result in more untreated fever and pain
  - Consistent with the following:
    - EMA's PRAC which recommended "no action"
    - ACOG which stated there is "no direct relationship between acetaminophen use and behavioral issues in children"
- Cons:
  - Additional publications are likely
  - Association could be causal

Summary

- Acetaminophen is the first choice pain and fever reliever during pregnancy
- Eleven observational studies report some association with adverse neurodevelopmental outcomes
- Fully adequate pre-/post-natal developmental toxicity and early juvenile toxicology studies were not conducted, but may not be relevant in setting of clinical data, and Drug Facts does not contain this information
- Prior communications warn of risks associated with pain medicine use during pregnancy
- Epidemiological data do not support causal association. More studies are likely in the future, but the quality of the evidence is unlikely to change.
- Should we:
  - Release another similar communication, which could cause anxiety and shift usage patterns to NSAIDs or opioids
  - Conduct nonclinical study, noting limitations above and possible confounding hepatotoxicity
  - Close the TSI
- Opinion varies within the group, particularly between Clinical and Epidemiology.
- What does the Medical Policy Council advise?

Backup slides

Overview of findings associated with prenatal APAP exposure

- IQ
  - 1 study: mean -3.4 IQ points (in absence of maternal fever)
  - 2 studies: no effect
- Motor development
  - 2 studies: delayed walking
    - Brandlistuen 2013: Adjusted beta coefficient for use 28+ days 0.24
    - Vlenterie 2016: Number needed to harm for delayed walking at 18 months = 48 (with 28+ days of exposure)
  - 1 study (Avella-Garcia 2016): no motor effects on Bayley at age 1
- General behavioral problems
  - 4 studies found higher prevalence of nonspecific problem behaviors (on parental ratings)
    - Brandlistuen 2013: increased behavior problems on Child Behavior Checklist age 3
    - Liew 2014: Increased "Total Difficulties" score age 7, Strengths and Difficulties Questionnaire
    - Stergiakouli 2016: Increased risk of high "Total Difficulties" score age 7 with exposure @ 32 wks
    - Thompson 2014: Higher "Total Difficulties" scores ages 7, 11

Overview of findings associated with prenatal APAP exposure, continued

- Autism
  - Case-control study: use of “antipyretics” (not specified) attenuated risk of autism with maternal fever during pregnancy
  - 1 study: autistic signs/symptoms increased in males, lower in females
  - 1 study: increased risk of diagnosis of autism spectrum disorder
- ADHD
  - 1 out of 2 continuous performance task studies found increased errors
  - 2 studies found modest associations with Hyperkinetic Disorder
  - 1 study found more use of ADHD drugs
  - 3 studies showed some elevation in ADHD symptom ratings
- Language
  - 1 study showed communication problems
  - 1 study showed language delay

Study	Major findings for prenatal APAP exposure versus unexposed (significant findings shaded)	Strategies to control for confounding
Avella-Garcia 2016	Increased ADHD symptoms and continuous performance task errors. No significant associations with cognitive, motor, social development. In males, dose-related increase in reported autistic signs/symptoms; in females fewer symptoms	APAP indications of chronic illness, analgesia, fever were adjusted for (or excluded in a sensitivity analysis)
Liew 2016	Mean -3.4 IQ points in absence of maternal fever	Assessed interaction between fever and APAP use. Analysis adjusted for maternal IQ, EtOH, tobacco use
Streissguth 1987	No significant association with IQ (aspirin associated with lower IQ). No effect on video vigilance task (aspirin exposure associated with more errors)	Adjusted for maternal use of EtOH, nicotine, caffeine, antibiotics, other covariates relevant to IQ
Liew 2014, 2016	Increased risk for Hyperkinetic Disorder (HR 1.4, 95% CI 1.2-1.6) Increased risk of use of ADHD drugs (HR 1.3, 95% CI 1.2-1.4) Increased risk of autism spectrum disorders	Covariates incl. maternal infection/inflammation, fever, musculoskeletal disease, smoking, maternal mental health, childhood behavior problems of parents. Covariates incl. sex, year, maternal age, parity, socioeconomic status, smoking, alcohol, maternal BMI, maternal mental health problems, folic acid intake, fever, skeletomuscular problems, use of ibuprofen and aspirin
Stergiakouli 2016	Increased risk of SDQ hyperactivity score 7+ (HR 1.2, 95% CI 1.0-1.4)	Adjusted for maternal infections, musculoskeletal problems, headaches. Assessed association with maternal postnatal and partner's APAP use.
Thompson 2014	Elevated Conners (ADHD) subscales	Analysis adjusted for multiple covariates, incl. antenatal maternal perceived stress, living with biological father and activity level at age 3.5, high fever during pregnancy
Brandlistuen 2013	At age 3, significantly more psychomotor problems and behavioral problems on Child Behavior Checklist	Unexposed siblings as control group. Ibuprofen analyzed for comparison. Adjusted for maternal fever, infection, co-medication exposures
Vlenterie 2016	Delayed walking at 18 months	PS matching; stratification by maternal headache/migraine, fever, infection.
Ystrom 2017	Increased risk for Hyperkinetic Disorder (HR 2.2, 95% CI 1.5-3.2 with 29+ days exposure)	No association with APAP use preconception, but association with paternal use suggests residual confounding
Bornehag 2017	OR for language delay at 30 months with highest exposure = 10.3 (1.4-77.9) in girls (no association in boys)	Adjusted for maternal education, maternal weight, smoking, enrollment week.

Autism

Study	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	In males, dose-related increase in reported autistic signs/symptoms; in females fewer symptoms
Zerbo 2013	Maternal fever associated with autistic spectrum disorders, antipyretic use attenuated association
Liew 2016	For >20 wks use, HR for autistic spectrum disorders 1.62 (1.05-2.51).

ADHD

Study	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	More ADHD symptoms, more errors on continuous performance task , age 5
Liew 2014	Hyperkinetic Disorder: HR 1.4, 95% CI 1.2-1.6 Use of ADHD Drugs: HR 1.3, 95% CI 1.2-1.4
Stergiakouli 2016	SDQ Hyperactivity score 7+: HR 1.2, 95% CI 1.0-1.4
Streissguth 1987	No association (aspirin exposure associated with more errors)
Thompson 2014	Elevated Conners subscales, but not elevated overall ADHD index
Ystrom 2017	Hyperkinetic Disorder: HR 2.2, 95% CI 1.5-3.2 for 29+ days exposure

IQ

Study	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	No association
Liew 2016	Mean -3.4 points in absence of maternal fever
Streissguth 1987	No association (aspirin was associated with lower IQ)

Reference ID: 4211689

Motor development

Study	Finding for prenatal APAP exposure versus unexposed
Avella-Garcia 2016	No associations age 15 mos or 5 yrs
Brandlistuen 2013	Associated with psychomotor problems age 3
Vlenterie 2016	Delayed walking 18 mos

Language

Study	Finding for prenatal APAP exposure versus unexposed
Bornehag 2017	Associated with language delay age 30 months
Brandlistuen 2013	Associated with communication problems age 3

General behavior rating scales

Study	Outcome	Finding for prenatal APAP exposure versus unexposed
Brandlistuen 2013	Child Behavior Checklist age 3	Increased behavior problems
Liew 2014	Strengths and Difficulties Questionnaire age 7	Increased risk SDQ "Total Difficulties" score
Stergiakouli 2016	Strengths and Difficulties Questionnaire age 7	Increased risk of high "Total Difficulties" score (later pregnancy exposure)
Thompson 2014	Strengths and Difficulties Questionnaire ages 7, 11	Increased Strengths and Difficulties scores

Reference ID: 4211689

Exposure-risk relationship

Study	Outcome	Exposure-risk relationship
Avella-Garcia 2016	Hyperactivity/Impulsivity age 5 (incidence rate ratio)	2.01 (0.95-4.24) for use in 3 trimesters; 1.37 (0.97-1.92) for use in 1 or 2
Brandlistuen 2013	Psychomotor, behavior problems age 3	Stronger associations with 28+ days exposure vs. <28 days
Liew 2014	Hyperkinetic disorder age 7	Any exposure: HR 1.4 (1.2-1.6) 20+ wks exposure: HR 1.8 (1.4-2.5)
Liew 2016	Autistic spectrum disorders	Trend for higher HR by more weeks of acetaminophen use (p-trend = 0.006)
Vlenterie	Motor delay, communication problems	Only associated with exposure of 28+ days
Ystrom 2017	Hyperkinetic disorder	HR increased monotonically with increasing total days of exposure
Bornehag 2017	Language delay at 30 months	OR for top quartile:bottom quartile urine acetaminophen 10.3 (1.4-77.9)

Liew 2016

- Danish National Birth Cohort
- 1491 mothers interviewed at 12 & 30 wks and 6 months post-partum
- Collected data on pain relievers used, fever, infection/inflammation, muscle/joint pain
- Adjusted for maternal IQ and other covariates
- Outcome: IQ testing age 5

Liew 2016, results

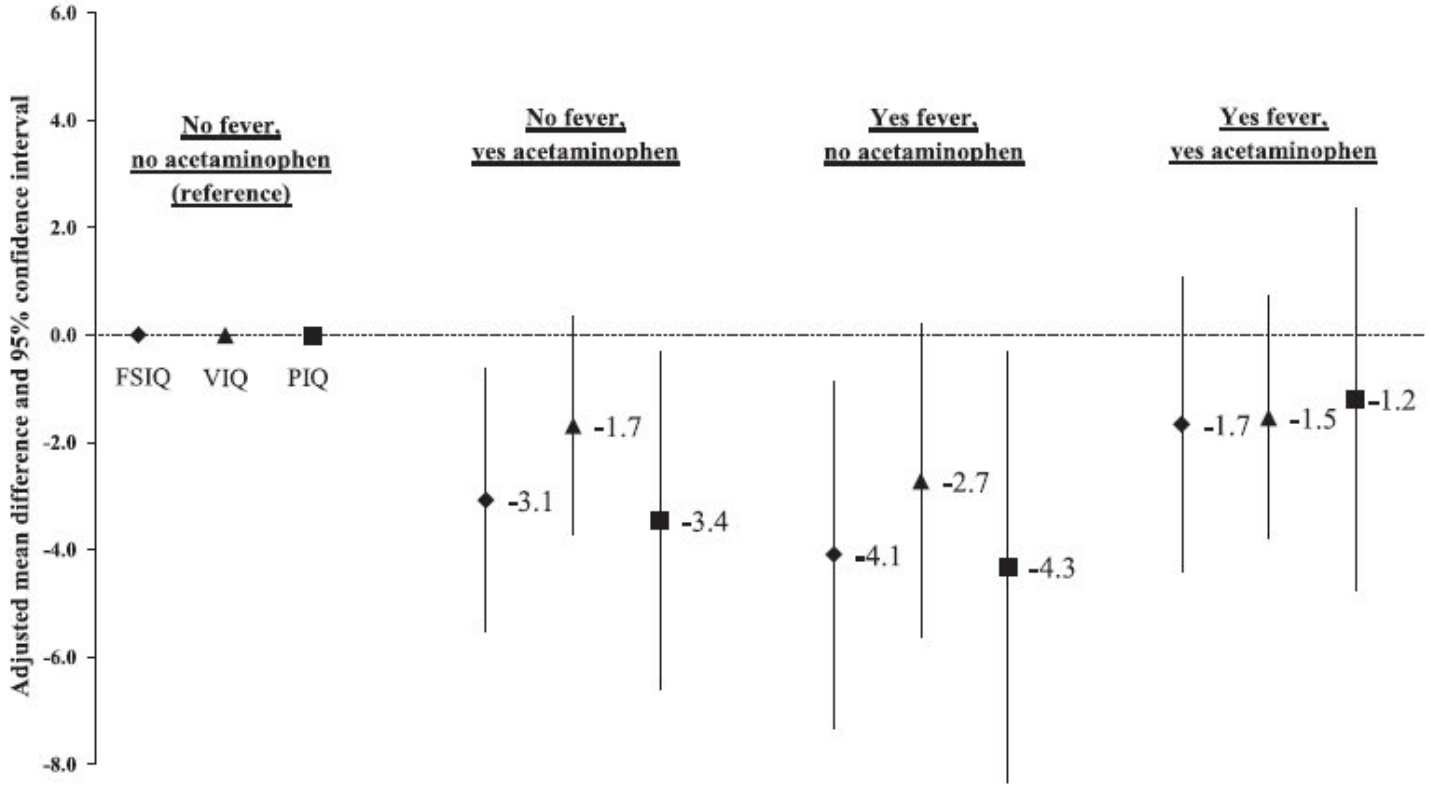


FIGURE. Association between prenatal use of acetaminophen, maternal fever and child's FSIQ, VIQ, or PIQ. Mean differences and 95% CIs adjusted for parental education, maternal IQ, maternal smoking and drinking during pregnancy, parity, maternal age at child birth, child's sex, and prenatal use of ibuprofen or aspirin. Interaction *P* values between acetaminophen and fever for FSIQ, VIQ, and PIQ are 0.01, 0.13, and 0.02, respectively. FSIQ indicates full-scale IQ; PIQ, performance IQ; VIQ, verbal IQ.

Liew 2016 study: strengths and limitations

- Strengths
  - Psychologists administered all cognitive testing
  - Exposure defined prospectively (avoids recall bias)
  - Analysis stratified on fever, inflammation/infection, muscle/joint problems
  - Analysis adjusted for parental education, maternal IQ, maternal smoking and drinking, parity, maternal age, gender, prenatal use of ibuprofen or aspirin
- Limitations
  - Timing of fever relative to APAP use uncertain
  - Lack of statistical precision
  - No adjustment for postnatal covariates
  - Possible unmeasured confounding
  - Sample excluded children with severe developmental delay

Brandlistuen et al. 2013

- Source: Norwegian Mother and Child Cohort
- 939 same sex sibling pairs discordant for in utero APAP exposure
- Follow up age 3 years
- Covariates included fever, infections, concomitant medications, smoking, alcohol, allergy, asthma, rheumatism, maternal depression
- Outcomes: psychomotor development, behavior ratings (Child Behavior Checklist; Emotionality, Activity & Shyness questionnaire)

Brandlistuen 2013: strengths and limitations

- Strengths
  - Analysis of same-sex sibling pairs provides strong control for many covariates
  - Greater association with long-term use
  - No significant associations with ibuprofen pregnancy exposure
  - Analysis adjusted for fever, infection, back pain, concomitant medications
- Limitations
  - Possible unmeasured confounding
  - Ibuprofen-exposed sample small, point estimate suggested effect
  - Clinical diagnoses not assessed (difficult at age 3)
  - Dose not available

Brandlistuen 2013, results

(Reference=concordant use sibling pairs)
(*=statistically significant)

	Discordant on use ⩾28 days (No. of pairs = 134)	
	Crude β (95% CI)	Adjusted[a] β (95% CI)
Psychomotor problems		
Motor milestone	0.24 (0.06–0.42)*	0.26 (0.06–0.45)*
Gross motor	0.31 (0.12–0.50)*	0.24 (0.12–0.51)*
Fine motor	0.07 (-0.08–0.22)	0.05 (-0.12–0.21)
Communication	0.22 (0.03–0.41)*	0.20 (0.01–0.39)*
Behaviour problems		
Externalizing	0.24 (0.12–0.37)*	0.24 (0.12–0.37)*
Internalizing	0.14 (0.01–0.28)*	0.14 (0.01–0.28)*
Temperament problems		
Emotionality	0.10 (-0.04–0.24)	0.10 (-0.04–0.24)
Activity	0.23 (0.10–0.36)*	0.22 (0.11–0.36)*
Sociability	-0.01 (-0.15–0.13)	-0.01 (-0.15–0.13)
Shyness	0.01 (-0.14–0.15)	0.01 (-0.04–0.24)

Developmental neurotoxins can induce a spectrum of outcomes

Developmental Neurotoxin	Outcomes associated with prenatal/early childhood exposures
Lead	Decreased IQ, poor school performance, impulsivity, attention deficits
Methylmercury	Attention, sensory and motor deficits
PCBs	Neurobehavioral and cognitive deficits
Ethanol	Motor impairments, learning disabilities, impulsivity, memory impairment, attention deficits
Ionizing radiation	Decreased IQ, language disorders, decreased school performance, emotional disorders

Mendola et al. MRDD Research Reviews 2002;8:188–197.
Johnson et al. J Dev Behav Pediatr 0:1–5, 2017

TABLE. STUDIES OF NEURODEVELOPMENTAL OUTCOMES FOLLOWING IN UTERO ACETAMINOPHEN EXPOSURE

Abbreviations for relative risk measures: HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; RR, risk ratio

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
Avella-Garcia 2016	To determine if prentatal APAP exposure adversely affects neurodevelopment at 1 and 5 years of age	Longitudinal, prospective birth cohort study	Infancia y Medio Ambiente project in 3 regions of Spain, 2004-8	Mothers eligible if 16+ years old, carrying singleton pregnancy, & planning to give birth at participating hospital	Medications (including APAP) used during pregnancy or 1 mo. before determined by interview at pregnancy weeks 12 and 32. Exposures after week 32 interview not ascertained.	Bayley scale of infant development at age 15 months. McCarthy IQ scale, CPSCS, CAST, DSM-IV criteria for ADHD, Conners K-CPT at age 5	2195 children age 1 yr, 2001 children age 5 yrs	Multivariable linear regression or negative binomial regression; outcomes were continous variables. Multiple covariates evaluated including chronic illness, fever, UTI.	After adjustment, APAP exposure associated with significantly more hyperactivity/impulsivity ADHD symptoms, K-CPT commission errors, and in males only, autistic symptoms. No significant effects on cognitive measures, social competence scale scores. Suggestion of increased risks with greater frequency of use. IRR for increased hyperactivity & impulsivity symptoms 1.41 (95% CI 1.01-1.98)
Brandlist-uen 2013	To examine psychomotor, behavioral and temperament outcomes with prenatal APAP exposure at age 3 yrs	Population-based prospective cohort study	Norwegian Mother and Child Cohort Study, 1999-2008	Mothers from anywhere in Norway recruited into cohort at time of their gestational week 17 ultrasound. This analysis limited to same gender sibling pairs	APAP exposure, frequency, indication ascertained by questionairres (at 17 wks and 30 wks gestation, and 6 mos postnatal. Ibuprofen exposure similarly ascertained as comparator	ASQ for psychomotor development, CBCL for behavioral problems, EAS for temperament	2919 same-sex sibling pairs, of whom 939 were discordant for prenatal APAP exposure. 155 discordant sibling pairs for ibuprofen exposure.	Generalized linear regression to calculate beta coefficients. Data on fever, infection, concomitant exposures assessed for inclusion in model.	APAP exposure of 28+ days associated with delayed gross motor development, delayed communication, externalizing and internalizing behaviors, higher activity. No statistically significant effects of ibuprofen exposure, though motor milestones showed p-values <0.10. Linear regression only, no relative risks

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
Liew 2014	To evaluate whether prenatal APAP exposure increases the risk of ADHD	Population-based prospective cohort study	Danish National Birth Cohort, 1996-2002	Danish-speaking mothers of singleton infants who responded to 3 phone interviews (at 12 and 30 wks gestational age and 6 mos postpartum)	Use of APAP and other painkillers by gestational week reported during telephone interviews (at 12 and 30 wks gestational age and 6 mos postpartum)	At age 7: prescriptions for ADHD drugs, diagnoses of Hyperkinetic Disorder, SDQ	N=64322 for diagnosis and ADHD drug use; 40916 of these with SDQ data	Cox proportional hazards regression for ADHD outcomes; generalized linear models for SDQ. Covariates incl. maternal infection/inflammation, fever, musculoskeletal disease, smoking, maternal mental health, childhood behavior problems of parents. Reference=children w/o prenatal exposure	At age 7: Hospital diagnosis of hyperkinetic disorder, with any APAP exposure, HR = 1.37 (1.19-1.59); with APAP exposure for 20+ weeks of pregnancy, HR 1.84 (1.39-2.45). Use of ADHD medications, HR = 1.29, (1.15-1.44) for any exposure and 1.53 (1.21-1.94) for 20+ weeks exposure. For ADHD-like behavior (SDQ total difficulties score 17+), RR=1.13 (1.01-1.27) for any exposure, and 1.46 (1.16-1.85) for 20+ weeks exposure
Liew 2016a	To examine whether prenatal use of APAP affects offspring's IQ	Population-based prospective cohort study	Danish National Birth Cohort, 1996-2002	"Lifestyle During Pregnancy Study" of women selelcted from the Danish National Birth Cohort, with children 5 years old, Sep 2003-Jun 2008, oversampled for EtOH use	Use of APAP and other painkillers by gestational week reported during telephone interviews (at 12 and 30 wks gestational age and 6 mos postpartum). Fever, infection/inflammation, muscle/joint pain determined at 30 wks	IQ (on WPPSI-Revised version)	1491 mothers and children	Linear regresssion adjusted for maternal IQ and other covariates. Reference = mothers with no fevers or APAP during pregancy	Children of mothers who used APAP during pregnancy and did not have fever had performance IQs lower by 3.4 (0.30-6.6) points on avg; fever without APAP lowered both verbal and performance IQ, but no significant effect of APAP in mothers who had fever No relative risks

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
Liew 2016b	To examine whether in utero APAP exposure affects attention and executive function at age 5 years	Same as above	Same as above	Same as above	Same as above	Test of Everyday Attention for Children at Five (TEACh-5) administered by psychologists. Behaviour Rating Inventory of Executive Function (BRIEF) by parents and teachers	1491 (same as above)	Calculated OR for attention or executive function one standard deviation below the mean, adjusted for multiple potential confounders	For subnormal overall attention, OR 1.5 (1.0, 2.5); for selective attention difficulties, OR 1.5 (1.0, 2.4); for parent-rated subnormal executive function, OR 1.5 (0.9, 2.3).
Liew 2016c	To investigate whether in utero APAP exposure increases risk for autism spectrum disorders (ASD)	Same as above	Same as above	Danish-speaking mothers of singleton infants who responded to 3 phone interviews (at 12 and 30 wks gestational age and 6 mos postpartum)	Same as above	Hospital admissions with diagnosis of ASD after an average of 12.7 years follow-up	N=64322 live born children	Cox PH adjusted for sex, year, maternal age, parity, socioeconomic status, smoking, alcohol, maternal BMI, maternal mental health problems, folic acid intake, fever, skeletomuscular problems, use of ibuprofen and aspirin	For >20 wks use, HR for ASD 1.62 (1.05-2.51). Stronger association for ASD with hyperactivity
Stergiak-ouli et al. 2016	To examine associations between behavioral problems and prenatal APAP exposure	Longitudinal, prospective birth cohort study	Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2, Bristol, UK	Any pregnant woman from the study region with due date between April 1, 1991 and December 31, 1992	Prenatal APAP exposure assessed by questionnaire, at 18 and 32 weeks of gestation and when child was age 61 months	SDQ at age 7 years	7796 mothers	Generalized linear models to estimate risk ratios adjusted for multiple covariates, including maternal EtOH and tobacco use, psychiatric history, infections, musculoskeletal symptoms, migraine, headache.	RR for SDQ total difficulties (score≥ 17): not significant at 18 wks, 1.37 (1.07-1.75) at 32 wks. RR for SDQ hyperactivity score ≥ 7: 1.18 (1.01-1.38) for exposure at 18 wks, 1.22 (1.04-1.43) for exposure at 32 wks.

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
Streiss-guth et al. 1987	To provide an exploratory analysis of neurodevelopmental teratogenicity of APAP and ASA	Logintudinal prospective pregnancy cohort study	Seattle Longitudinal Prospective Study on Alcohol and Pregnancy, 1974-5	Consecutive pregnant women receiving prenatal care	—Prenatal use of ASA and APAP assessed at month 5 by maternal interview	IQ (WPPSI) and video vigilance task	421 children assessed at 4 yrs, 3 mos	Multiple regression, including maternal alcohol, nicotine, caffeine, and antibiotic use, and various covariates that affect IQ	—ASA exposure negatively correlated with IQ and with errors on vigilance task. No correlations with APAP exposure. No relative risks reported
Thompson et al. 2014	To assess the reported association between prenatal exposure to APAP and ADHD.	Longitudinal cohort study	Aukland Birthweight Collaborative Study of children born Oct 1995- Nov 1997	In the catchment area, all small for gestational age (SGA) infants (in the tenth percentile) and an approximately equal number of other fullterm infants selected randomly	Prenatal exposure to APAP (yes/no), as reported by mothers during interview shortly after birth	SDQ and Conners Behavior Rating Scale, at 7 and 11 years of age	N=614 for SDQ, N=617 for Conners	Multivariable general logistics model for difference in scores, multiple risk factors for ADHD as covariates, including maternal smoking, alcohol use, high fever, psychiatric history	Statistically significantly higher adjusted Total Difficulties scores on SDQ for APAP-exposed children. Elevations on certain subscales of Conners but not on ADHD index. No relative risks reported.
Vlenterie 2016	To investigate neurodevelop-mental problems following prenatal exposure to APAP in children age 18 mos.	Prospective cohort study	Norwegian Mother and Child Cohort Study, 1999-2008	Mothers from anywhere in Norway recruited into cohort at time of their gestational week 17 ultrasound.	APAP exposure, frequency, indication ascertained by questionnaires (at 17 wks and 30 wks gestation, and 6 mos postnatal.	ASQ, EAS and CBCL, age 18 mos.	1630 propensity score matched pairs (28+ days of APAP vs. no APAP)	Propensity score matched OR	Delayed motor milestone (walking) OR 1.35 (1.07-1.70) & communication problems OR 1.38 (0.98–1.95) with 28+ days prenatal APAP exposure, no other significant associations
Ystrom 2017	To assess the association between maternal use of APAP during pregnancy and attention deficit hyperactivity disorder (ADHD) in offspring	Prospective cohort study	Norwegian Mother and Child Cohort Study (births 1999-2009)	Same as above	Same as above	ICD 10 diagnosis of hyperkinetic disorder	112973 children, 2246 with hyperkine-tic disorder	Cox proportional hazard, with stratification for indications and duration of use	For 29+ days of use, HR 2.2 (1.5-3.2)

Study	Objectives/Aims/ Scope	Design	Data Source	Subject selection criteria	Exposure	Outcome(s)	Sample Size	Statistical Analyses	Study Results
Bornehag 2017	To examine prenatal APAP exposure and language development	Prospective cohort study	Swedish Environmental Longitudinal Mother and child, Asthma and allergy study	Swedish pregnant women in the county of Varmland, 2007-2010, recruited at first prenatal visit	At first prenatal visit, (1) women estimated APAP taken since start of pregnancy, and (2) provided urine sample for urinary APAP concentration	Language delay=fewer than 50 word vocabulary age 30 mos.	754	Multiple logistic regression; APAP urinary concentration analyzed by quartile	Number of APAP tablets used and urine APAP associated with language delay in girls, not boys. For highest quartile of urine APAP, adjusted OR for language delay (girls) = 10.3 (1.4-77.9)

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/s/

JANICE ADAMS
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